

### **REMARKS**

In an office action mailed September 28, 2009, claims 26-39 have been rejected. In response, Applicants have amended claims 26, 32, 33 and 40, cancelled claims 30 and 31, and have added new claim 41. Consequently, claims 26-29, and 32-41 are pending examination.

Claim 40 had previously been withdrawn by the Examiner. As of the herein amendment, claim 40 has been amended to depend from claim 34, and therefore reads on the elected species. New claim 41 further defines the features of claim 26. No new matter has been added.

Entry of the herein amendments and remarks is respectfully requested.

### **Rejections Under §102**

Claims 26-27, 34, and 39 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Fueyo et al. as evidenced by Nevins. Applicants respectfully traverse the rejection.

As argued in Applicants' previous response, the adenoviral genome disclosed by Fueyo et al. does not comprise a coding sequence of at least one mammalian restoring factor, as is required for the adenovirus of claim 26.

Contrary to the Examiner's statements in the pending Office Action, Fueyo et al. does not disclose, implicitly or inherently, an adenoviral genome comprising p53 or a p53 derivative.

Applicants are unable to identify where in Fueyo et al. an adenoviral genome comprising p53 or a p53 derivative is disclosed. If the rejection is maintained, it is respectfully requested that the Examiner point Applicants to the parts of Fueyo et al. that support disclosure of an adenoviral genome comprising p53 or a p53 derivative.

The Examiner refers to the statement in Fueyo et al. that the “ $\Delta$ 24 adenovirus induced cell death even in mutant-p53 cells” (page 7). However, this statement does not suggest that the Fueyo et al. adenovirus comprises p53. The production of the  $\Delta$ 24 adenovirus is described in the Materials and Methods section on page 8. Nothing in the section teaches or suggests that the adenovirus comprises p53 a p53 derivative, or any other mammalian restoring factor.

The Examiner further states on page 6 of the Office Action that in Fueyo et al. “the p53 apoptosis pathway is restored by expression of the mutant E1A protein”. This statement appears to contradict the Examiner’s previous statements that the Fueyo adenovirus restores p53 apoptosis by expressing a p53 gene. In addition, the mutant E1A protein of Fueyo et al. is a viral protein and is not a **mammalian** restoring factor as required by the claims.

Furthermore, nothing in Fueyo et al. discloses that the p53 dependent apoptosis pathway is restored. The 24 base pair E1A deletion, as disclosed in Fueyo et al., is not able to bind Rb (see abstract of Fueyo et al. and page 3, right column, lines 3-6). Therefore, expression of this mutant E1A protein will not induce the release of E2F from existing Rb-E2F complexes. The

lack of release of E2F, and hence the lack of activation of E2F, will not result in activation of the p53 pathway, as is evidenced by Nevins.

Therefore, the mutant E1A as disclosed by Fueyo et al. is not able to restore the p53 apoptosis pathway because said protein can not bind Rb. The reported cell death of mutant p53 cells by the  $\Delta 24$  adenovirus is thus not mediated by restoration of the p53-mediated apoptosis pathway.

A claim is anticipated only if each and every element of the claim is found in a single prior art reference. In contrast to the statements in the pending Office Action, the adenovirus described in Fueyo et al. **does not satisfy the structural limitations of the claims**. As the Fueyo et al. reference, alone or in view of Nevins, does not disclose each and every element of the pending claims and thus fails to anticipate the pending claims. Reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

### **Rejections Under §103**

Claims 26-33 and 35-39 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chang et al. in view of Lin et al. Applicants respectfully disagree with the rejection. However, in an effort to expedite prosecution, claim 26 has been amended to specify that the virus genome further comprises a gene selected from a gene encoding the adenovirus

E1B-19kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof.

The Examiner alleges that it would have been obvious to a person of ordinary skill in the art to incorporate the tissue specific replication conditional control features of Chang et al. into the adenovirus p53 construct of Lin et al. and that there would have been a reasonable likelihood of success because the state of the art involving mutagenesis and adenoviruses were commonly practiced. Applicants strongly disagree.

As discussed in Applicants response filed June 24, 2009, the Examiner previously rejected the subject matter of claims 26 and 33 for non-enablement (see July 31, 2006 Office Action). The Examiner stated that the state of the art at the time the application was filed indicated that p53 dependent apoptosis is prevented through the action of the E1b proteins. The Examiner refers to Debbas and White, which states "E1B 19K and 55K proteins provide separate mechanisms that disable the cell suicide pathway of p53." The Examiner further cites to Blaho et al. which states that "the E1b 19 kDa protein functionally substitutes for the activity of Bcl-2 while the E1b 55 kDa binds p53 and inhibits its functions." Blaho et al. further states that cells which contain viral anti-apoptotic activities, such as those conferred by the adenovirus E1b region, are resistant to [virally] induced cell death". The Examiner relies on Querido et al. for teaching that E4orf6 and E1b-55kDa proteins function together to reduce the half-life of p53 and induce efficient p53 degradation.

Applicants agree with the Examiner's conclusion that the state of the art at the time the application was filed indicated that **p53 dependent apoptosis is prevented through the action of the E1B proteins**. Therefore, a person skilled in the art could not reasonably expect that the adenoviruses comprising the genes for E1B proteins, such as E1B-19dDa and E1B-55dDa, would work in combination with a mammalian restoring factor functional in restoring the p53 apoptosis pathway. The references cited by the Examiner clearly teach a person skilled in the art that **the claimed adenoviruses would not work**.

It is respectfully submitted that the combination of Lin and Chang is only possible using the knowledge of the invention, i.e. the use of impermissible hindsight. The Examiner states in the outstanding Office Action on page 9 that hindsight is permissible "so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure". As discussed above, at the time the application was filed, the knowledge of one of ordinary skill in the art was that **p53 dependent apoptosis is prevented through the action of E1B proteins**. Combining the adenovirus p53 construct of Lin et al. with E1B proteins known to inhibit p53 dependent apoptosis is only possible using the teaching of Applicants' own disclosure. As discussed in Applicants' replies of January 1, 2007 and August 21, 2007, it is Applicants' disclosure that first demonstrated that E1B proteins, such as E1B-55kDa, not only fail to prevent apoptosis, but in fact **enhance oncolytic activity** in viruses comprising a

mammalian restoring factor. This surprising finding could in no way be predicted by the cited references.

The Examiner states on page 10 of the outstanding Office Action that “It is evident from both Lin and Chang and the much literature discussed during the course of the multi-year prosecution of this application that p53 can and is used in replication competent recombinant adenoviruses”. Applicant strongly disagrees. Chang does not disclose the use of p53, Lin does not disclose replication competent adenoviruses, and Applicant has clearly demonstrated that a person skilled in the art would not have an expectation of success in combining Chang and Lin. The Examiner is requested to cite specifically to literature that demonstrates that p53 was used in replication competent recombinant adenoviruses before Applicants’ invention.

According to MPEP §2143(G):

The rationale to support a conclusion that the claim would have been obvious is that “a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success.” *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006). If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. MPEP 2143

Applicants submit that one of skill in the art would not have been motivated to combine the p53 adenovirus of Lin with an adenovirus encoding an E1B-19kDa or E1B-55kDa protein as these proteins were known to disable the cell suicide pathway of p53. Furthermore, as the state

of the art indicated that p53 dependent apoptosis is prevented through the action of the E1B proteins, a skilled person would not have had a reasonable expectation of success. Therefore the obviousness rejection cannot stand on this rationale. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

It is now believed that the application is in condition for allowance. If the Examiner believes a telephone discussion would be beneficial to resolve any outstanding issue, he is invited to contact the undersigned without hesitation.

Respectfully submitted,

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